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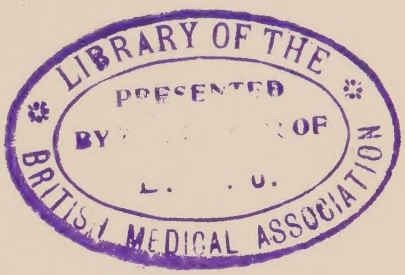
in the treatment of

Pulmonary Tuberculosis.

BY

JOHN R. GILLESPIE.

With the author's compliments.



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— BY —

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THE USE OF TUBERCULIN
IN THE
TREATMENT OF PULMONARY TUBERCULOSIS

At present medical practitioners hold very diverse opinions in regard to the advisability of using tuberculin in the treatment of pulmonary tuberculosis. Some regard it as helpful, some as useless, and some as injurious.

This is not to be wondered at when one considers how varied are the ways in which tuberculin has been administered, even by those who, by reason of the number of cases treated by them, are regarded as experts in its use.

It is the purpose of this paper to set forth a rational method of administering tuberculin in cases of pulmonary tuberculosis, which has given good results in the hands of myself and my assistants.

Tuberculin Reactions.

Let us first consider certain phenomena, which may ensue when tuberculin is injected subcutaneously into the human body.

In the case of some persons who are suffering from tuberculosis, the injection of a minute quantity of tuberculin, say ·0000001 c.c. of old Tuberculin, or less even, is followed, after a period of incubation varying from a few hours to two or three days, by some or all of the following "reactions":

1. *Local Reaction*—Indicated by redness, swelling and pain, round about the site of inoculation.
2. *General Reaction*—Indicated by impairment of the patient's sense of well-being, loss of appetite and of weight, and increase of pulse-rate.
3. *Temperature Reaction*—Indicated when slight by a diminution in the daily range of the patient's temperature, which is commonly called "flattening of the temperature chart," or by a rise in the daily maximum temperature without its exceeding 99°F.; when greater,

by his temperature rising above 99°F. This greater temperature reaction I call "Febrile Reaction."

N.B.—Throughout this paper "temperature" is to be understood as meaning "mouth temperature."

4. *Focal Reaction, i.e.*—Hyperæmia at the site of disease, with increase of discharge, if any. Hyperæmia is readily observed in cases where the lesion is in the skin. In pulmonary cases focal reactions, when sufficiently great, can be demonstrated by increased "physical signs,' and by increase in the quantity of sputum.

If the reactions have not been too great, the indications of local and temperature reactions disappear in a day or two, and those of general and focal reactions may become reversed, the patient feeling better than before he got the injection, the appetite being improved, the weight increased, and the pulse-rate diminished: hyperæmia, when observable, is found to be succeeded by comparative pallor, and by signs of healing of the lesion; and discharges, and "physical signs" in lung cases, may be diminished.

In the case of other persons who are suffering from tuberculosis, however, the injection of so small a quantity of tuberculin may be followed by none of these reactions, in order to produce which, the dose may have to be multiplied hundreds or thousands or myriads of times, but the reactions *can* be produced by giving a sufficiently large dose. Further, it is found that the condition of this latter class of persons in regard to tuberculin can be brought about artificially in the case of the former class, by the administration of gradually increasing doses, given at suitable intervals, the amount of tuberculin that can be tolerated being thus gradually increased. This gradually increasing tolerance of tuberculin can be produced by doses slightly less than would be sufficient to produce local or febrile reactions, as well as, or even better than, by doses producing the same.

Toxin Theory.

All the above phenomena, as to which observers are agreed, point to the action of a toxin ; a toxin being a poisonous substance of unknown composition, requiring an incubation period before it manifests itself, and bringing about, when introduced into the body of an animal in non-lethal doses, the production of a body that is an antidote to itself, called its anti-toxin. Whatever degree of tolerance of tuberculin is possessed by a person who has suffered from tuberculosis, may be attributed to the presence of anti-toxin in his tissues, produced as the result of previous inoculations of tuberculin, either administered artificially, or admitted to the circulatory system from the patient's own lesion.

Modification of Toxin Theory Required.

But now another curious fact has to be considered, viz.—that in the case of persons who have never suffered from tuberculosis, large quantities of tuberculin, *e.g.*—·01 c.c. of Old Tuberculin, or more, can be injected subcutaneously without producing any apparent reaction. Now it is contrary to experience to find any signs of the presence of anti-toxin in the body, unless the anti-toxin has been either artificially bestowed, or produced in response to the stimulus of the corresponding toxin.

Wolff-Eisner Theory.

It is therefore reasonable to conclude that tuberculin does not itself contain the toxin which produces the local, general, febrile, and focal reactions which may follow its administration, but that there is in the tissues of persons who have suffered from tuberculosis some substance which, by reacting with something in the tuberculin, produces the toxin. Such substance, called by Wolff-Eisner, tuberculolysin, we shall, for convenience, call lysin.

The fact that test doses of tuberculin have never, to my knowledge, proved lethal, helps to confirm this theory. Chart I. serves to illustrate this point. The patient, W. T., was given a test dose of T. 0002 c.c. which caused a sharp

febrile reaction. After this had subsided the first treatment dose of P.T.O. ·000001 c.c. was given, and produced a febrile reaction almost as great. Now T. is from 50 to 100 times as strong as P.T.O., *vide infra*, so that the test dose was at least 10,000 times as great as the one that produced almost as great reaction. If the toxin were ready made in the tuberculin, one would expect that, in a patient so sensitive that the smaller dose produced so much reaction, a dose 10,000 times as great would have killed him. But the fact that he was not killed, or even injured seriously, is simply explained by the Wolff-Eisner theory, according to which the amount of lysin present sets a limit to the amount of toxin that can be produced from any dose of tuberculin however great.

Further confirmation of the Wolff-Eisner theory may be derived from another consideration. It is well known that toxins are, as a class, what is called thermolabile, *i.e.*—they are easily altered, so as to lose their toxicity, by heat; a temperature of 60° C. being usually sufficient for this purpose. Now in the preparation of Old Tuberculin it is subjected to the heating effect of steam at 100° C. for an hour, and yet powerful toxic effects result from its administration, which confirms the view that the toxin is not ready made at the time of the heating.

Factors to be Considered in the Rational Administration of Tuberculin.

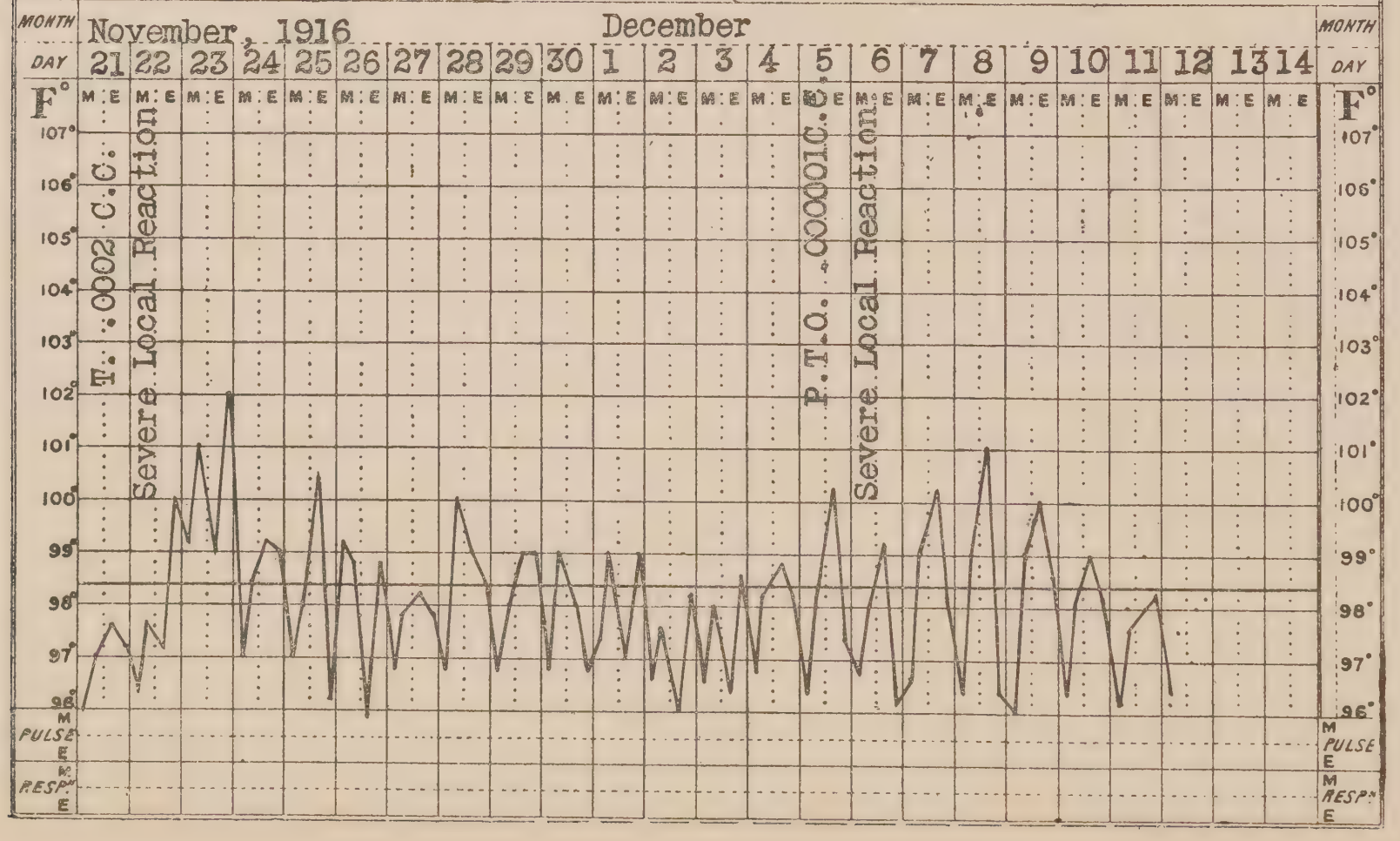
In the rational administration of tuberculin, then, we have to take into account—quantitatively as far as possible—the following factors :—

1. The Tuberculin, which can be measured by a pipette. The essential ingredient, whatever it be, will be in proportion to the quantity of tuberculin used, so long as one variety of tuberculin is adhered to.
2. The Lysin present in the patient's tissues.
3. The Anti-toxin present in the patient's tissues.

Temperature Chart, &c.

No. 1.

Name of Patient N.T.



The quantities of the last two can be estimated only indirectly, by comparison with the amount of tuberculin used, and observation of the effects produced.

The total toxin produced from a given dose of tuberculin will be the equivalent of the tuberculin or of the lysin, whichever be the less. Obviously it cannot be greater than either.

The free toxin produced will be the equivalent of the total toxin minus the anti-toxin, if this be a positive quantity. Otherwise there will be no free toxin.

Too Large Doses.

The maximum reactions will be obtained from the dose of tuberculin which is equivalent to the lysin present, the free toxin available for producing reactions being in this case the equivalent of lysin minus anti-toxin. If the dose of tuberculin be in excess of the lysin, no greater reactions will be produced, and the excess of tuberculin is apparently eliminated in a few days. But in this case the operator has no control over events, as the effects produced do not depend on the only item that he can regulate, viz.—the dose of tuberculin.

"Hypersensitiveness."

We are now in a position to give a simple explanation of a condition of affairs which sometimes arises during the administration of tuberculin to a patient, and which has been a puzzle to many workers. A certain dose of tuberculin having been given, and a febrile reaction produced, the same dose is repeated and a greater febrile reaction results. It may be repeated again and again with increasing reactions. This state of affairs has been attributed to "hypersensitiveness" on the part of the patient. But the proper inference is, not that there is anything abnormal on the part of the patient, but that the dose of tuberculin is in excess of the lysin, and that the latter has increased, as the result of each injection, faster than the anti-toxin. If one persist in repeating the same dose in these cases, as some workers do, it may happen that the lysin will increase till it is greater

than the equivalent of the dose of tuberculin, after which the total toxin produced by each dose will no longer increase : and, the anti-toxin increasing with each dose, the free toxin will now grow less with each dose, till it is no longer able to produce febrile reaction.

But it is not a wise procedure, as the severe reactions which may result from it may do much harm to the patient. It is better to follow this *Rule :—*

If a certain dose be followed by a febrile reaction, and its repetition by a greater one, reduce the dose.

Too Small Doses.

If the dose of tuberculin be less than the equivalent of the anti-toxin present, no free toxin will result, and of course no reactions, nor any stimulus towards healing of the lesion.

But the patient will not be *in statu quo ante.* For a portion of his lysin and anti-toxin will have been used up, without the liberation of any free toxin to act as a stimulus towards producing more of these substances, thus rendering him liable to have reactions from smaller doses than before.

This explains how it is that, in Bardswell's words, "by the frequent repetition of a dose of moderate amount, intolerance, or hypersensitiveness, as the condition is usually termed, is actually encouraged."

Useful Doses.

We thus see that at any particular time in a patient's history there are certain rather narrow limits within which the dose of tuberculin, to be of benefit, must lie. It should exceed the equivalent of the patient's anti-toxin, otherwise there will be no useful stimulus ; and it should not exceed it by much, lest the effects be injurious, or beyond control.

From which we may infer that the optimum dose is one that falls but little short of producing febrile reaction.

Aims of Tuberculin Therapy in Pulmonary Tuberculosis.

There are two distinct advantages that may be gained by a series of properly regulated doses of tuberculin :—

1. *Control of the Patient's Temperature.*

It is well known that patients with pulmonary tuberculosis are liable to have their temperature raised on taking any exercise more than they are accustomed to. This is because such exercise causes what is called "auto-inoculation," *i.e.*— an escape of tuberculin from the patient's lesion into his circulatory system, so that the rise of temperature is really a febrile tuberculin reaction.

By a suitable series of tuberculin doses the amount of anti-toxin in the patient's system may be increased to such an extent that the amounts of tuberculin received by auto-inoculation are negligible.

The patient may thus be freed from these, to him, capricious rises of temperature, often called "colds," associated with anorexia, wasting, night sweats and loss of strength.

Even in cases where the amount of lung impaired is very great, and undergoes no diminution as a result of the treatment, or even gradually increases, it is worth while thus to keep the temperature under control when this can be done, as it sometimes can. It adds greatly to the comfort of the patient, enables him to enjoy his food, to take exercise without interruption, and so to train himself up till, in many cases, he is able to return to work. Such patients undoubtedly live longer than they would have done, if the temperature had not been controlled, and the period of distressing invalidism before the end is greatly reduced.

2. *Healing of the Lesion in the Lung.*

It has been noted above that after mild tuberculin reactions there may be improvement in the patient's sense of well-being, appetite, weight and pulse-rate. These desirable results can be produced as well, or better, by a dose of tuberculin a little less than would produce "reactions."

With the means of observation at our disposal, it is beyond our power to observe, in cases of pulmonary tuberculosis, the healing effect of a single dose of tuberculin. But when the amount of destruction of lung is not great, one usually finds after a series of suitable doses given at suitable

intervals for three months or more, that the "physical signs" are diminished, and the sputum is less in quantity and contains less yellow matter, and fewer tubercle bacilli when these have been present.

By continuing the course of treatment one succeeds in some cases in abolishing all signs and symptoms of the disease: in other cases all symptoms may disappear, but the site of the healed lesion may be permanently marked by an area over which "prolonged expiration" is heard: in cases where there has been more destruction of lung tissue, there may be in addition dulness over the area, and possibly contraction of the chest wall.

In all such cases it is well not to assume that the lesion is perfectly healed, until at least three months after all signs and symptoms of active disease have ceased to be detected.

Selection of Cases for Tuberculin Treatment.

Assuming that the diagnosis of pulmonary tuberculosis has been made, the clinical thermometer may be relied on to indicate the advisability, or otherwise, of tuberculin treatment.

One should, of course, make sure that the thermometer to be used is correct. I buy for my practice at tuberculosis dispensaries, half a gross of thermometers at a time. On testing them against my own thermometer which has been standardised, I find that, as a rule, one or two out of every dozen have to be rejected as incorrect. The incorrect ones usually read too high, but occasionally the reverse.

Incorrect thermometers can of course be used quite well if one has them standardised, and always allows for the error. But this complication would make the recording of the correct temperature too difficult for most dispensary patients; so I reject all thermometers whose reading is incorrect. I also reject some thermometers because it is so hard to shake down the mercury in them that the effort required to do it would be too much for ordinary patients.

The patient, or a friend who lives with him, is shown how to take and record the temperature. If the patient be not at work, he is instructed to record his temperature at

8 a.m., noon, 4 p.m., and 8 p.m. : if he be at work, to record it before breakfast, before dinner and at 8 p.m. The same rule is adhered to all through a course of tuberculin treatment. The patient is supplied with a card, a reproduction of which is here shown, and at each visit to the dispensary the records on it are marked on the temperature chart which is kept at the dispensary. The charting of the temperature records is important, as it reveals alterations in the temperature curves which might not strike one on merely glancing at the card.

Down County Council (T.D.).

HOME TEMPERATURE CARD.

LEDGER No.

19..... ...	8 A.M.	NOON	4 P.M.	8 P.M.

CONTINUE ENTRIES ON OTHER SIDE.

If it be found, after a few days' observation, that none of the recorded temperatures exceeds 99° F., tuberculin treatment may be begun at once, no matter what the condition of the lungs may be, provided the patient be not *in extremis*. As has been mentioned above, even in cases where there has been extensive destruction of lung tissue, and one has little or no hope of cure being effected, the course of tuberculin may be of considerable benefit to the patient; and, if properly regulated, can do no harm.

If the temperature be found to exceed 99°F. at any time in the day, the patient is ordered to go to bed and stay there, resting as completely as possible, till the temperature has settled, *i.e.*, no longer exceeds 99°F. at any time in the day. When the temperature has settled, the patient is allowed to get up by successive steps.

The longer the period of rest in bed required to cause the temperature to settle, the slower must be the gradations by which the patient is brought back to activity.

If after a few days' rest in bed his temperature have ceased to exceed 99°F., he can usually be brought back in about the same number of days to taking as much exercise as he was taking before the rest in bed was begun.

But if some weeks' rest in bed be required before the temperature has settled, I prescribe the following :—

Graduated Exercises.

1. Sitting up in bed for a quarter of an hour in the forenoon, and again in the afternoon.
2. Sitting up in bed for half an hour in the forenoon, and again in the afternoon.
3. Getting up, dressing, and sitting up for one hour in the whole day.
4. Staying up two hours.
5. Staying up four hours.
6. Staying up eight hours.
7. Taking a walk of a quarter of a mile in the forenoon, and again in the afternoon.

If the patient feels tired after this or other exercise, he is to lie down for half an hour ; or, at least, to sit with the feet up and the back supported.

8. Walks of half a mile each, forenoon and afternoon.
9. Walks of a mile each, forenoon and afternoon.
10. Walks of two miles each, forenoon and afternoon.
11. Walks of three miles each, forenoon and afternoon.
12. Light work.
13. Full work.

In no case is the patient allowed to pass from any stage to the next until he has passed at least two successive days in the current stage without the temperature exceeding 99° F., and without fatigue.

If at any stage the temperature exceed 99° F., the patient is told to go back to bed till it settles, then to come up quickly to the point where he had left off, after which he is to proceed as if the interruption had not taken place.

After the temperature has settled, tuberculin treatment may be begun as soon as convenient. For example, if the patient be in a sanatorium, it may be begun while he is still confined to bed. But if he is to receive the injections at a dispensary, he must first reach the stage at which he can travel to the dispensary and back without causing the temperature to rise above 99° F. At whatever stage tuberculin therapy be introduced, the graduated exercises are to be proceeded with all the same.

In the case of patients whose temperature is found not to exceed 99° F. from the first, the graduated exercises are also employed, taking as starting point what the patient has recently been doing.

This method of using graduated exercises differs from that of Marcus Paterson. In common with his method it has the advantage of improving the tone of the patient's tissues in general, so that they are better able to produce anti-bodies and assist in throwing off the disease ; and in particular of strengthening his muscles, and so enabling him to enjoy movement and ultimately return to work. But the

exercises are not used with the object of giving the stimulus to recovery by the uncertain mechanism of auto-inoculation, this stimulus being given by injections of tuberculin which can be accurately gauged.

Hygienic—Dietetic Treatment.

Of course everything concerning the patient's general health needs to be enquired into, and all discovered obstacles to the recovery of perfect health removed, as far as possible, whether he is being treated with tuberculin or not. Oral sepsis and constipation are among the commonest of these obstacles. When they have been remedied, flatulence, and in females amenorrhoea, which are regarded by patients as of much greater importance, usually disappear. Headaches and night sweating usually disappear also when the bowels have been regulated and the temperature has become normal. If headaches persist thereafter the eyes should be tested; and if any error of refraction be detected, suitable glasses should be obtained and worn by the patient.

If the temperature run too high, and do not respond quickly to rest in bed, an antiseptic inhalation appears in some cases to be of assistance. Whether this is due to the antiseptic properties of the inhalation, or to its relieving the cough, or to the fact of something being done having a soothing mental effect on the patient, and so enabling him to rest better, I am not prepared to say. Possibly all three factors come into play.

If the cough be so severe as to cause vomiting or pain, or to interfere seriously with sleep, medicine to soothe the cough or assist expectoration should be prescribed. Otherwise the cough does not require special treatment.

Pain in the region of the affected part of the lung can be alleviated, or abolished, by applying mustard over this region till the skin is reddened, after which the patient should be kept in bed for a couple of days.

The room, or rooms, occupied by the patient should be dry and well ventilated, and should have good natural light, and, if possible, a southern aspect.

The patient should have a sufficiency of good, plain, nourishing food. If the body weight be below par, and the alimentary tract will tolerate it, it may be desirable that the quantity of food should be rather more than would suffice for a healthy person. But stuffing the patient with food is undesirable. He is better without any alcohol.

Varieties of Tuberculin.

In my opinion, there is no essential difference between the different varieties of tuberculin in the market but that of strength. In my own practice I now use only two varieties, viz., Old Tuberculin (human) and Tuberculin Bouillon Filtrate (bovine) denoted hereafter in this paper by the letters T. and P.T.O. respectively. I find that T. is from 50 to 100 times as strong as P.T.O. ; but, allowing for this difference of strength, any acquired degree of tolerance of the one means a corresponding degree of tolerance of the other. This I have verified in a large number of cases. In regard to other varieties of tuberculin my experience is comparatively meagre : but several cases have occurred in which patients who had been receiving tuberculin injections of some other variety, have come for continuation of treatment, and been given P.T.O. or T. . In such cases, where a high degree of tolerance had been acquired for the other tuberculin, there was also a high degree for P.T.O. or T. .

Initial Dose.

As a general rule I now begin with P.T.O. ·000001 c.c. This hardly ever produces any local or febrile reaction ; but in some odd cases it does. In these cases, if the reaction be severe, the dose is reduced at the next injection : but if slight, the same dose is repeated. If after the second injection the reaction be greater than after the first, the dose is reduced, in accordance with the rule given above under the heading "hypersensitiveness." The lowest point to which I have ever had to reduce the dose was ·0000001 c.c. of P.T.O. .

If the reaction after the second injection be no greater than that which followed the first, the same dose is repeated

till no febrile reaction results from it ; after which increase of the dose is begun.

If, as is often the case, there be no appreciable result from the first injection, the dose is doubled each time until there is some local or temperature reaction, after which the procedure is similar to what has been recommended when the first dose caused reaction. By proceeding as above one soon arrives at what is a beneficial dose for the patient, with no danger of doing harm by a succession of too large doses, and the least waste of time while giving too small doses. Of course, if the initial dose be followed by satisfactory results such as increase of weight and improvement of pulse rate, or if there be " flattening of the temperature chart," or the temperature chart after the injection have the form of a wave whose highest point does not exceed 99°F., gradual increase of the dose is begun at once.

Intervals Between Doses.

Having arrived at a dose which is beneficial to the patient, two courses are open to us—

1. We may wait for such a length of time before giving another dose, that the amount of anti-toxin in the patient's tissues has subsided to about the same level as it stood at before the last injection, and then repeat the same dose, as suggested by Sir Almroth Wright.

2. We may give the next dose after a shorter interval, when, the anti-toxin in the patient's tissues having increased as the result of the last injection, a larger dose of tuberculin will be needed to produce the desired stimulus. This is the method first introduced by Koch, and commonly called the intensive method.

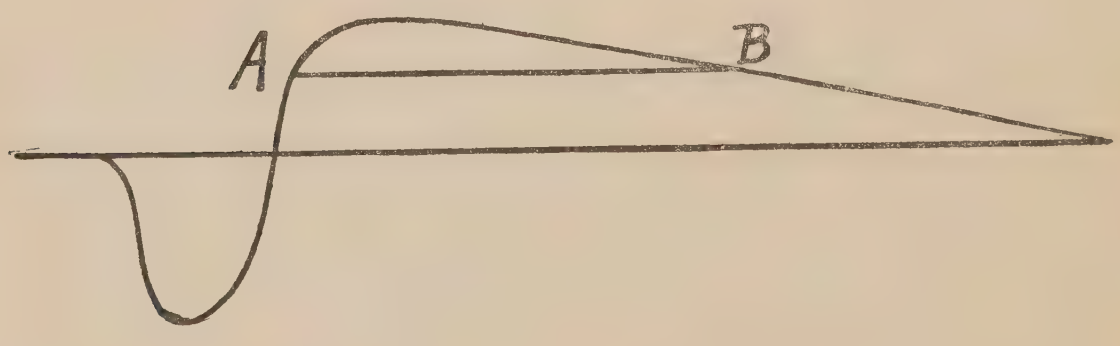
Wright's method, which has proved useful in many varieties of non-pulmonary tuberculosis, has proved disappointing when tried in pulmonary cases, probably because

(1) it fails to control the temperature, and (2) owing to the disturbing effects of auto-inoculations, the optimum dose does not remain constant, but varies in a way that cannot be calculated.

But after we have raised the patient's anti-toxin to such an amount that auto-inoculations have become negligible, these objections no longer hold good; and then, in my opinion, the best results are obtained by lengthening the interval between the doses so as to approximate to Wright's method.

In order to explain the reason underlying this opinion, let us employ the terms negative phase and positive phase in reference to the patient's anti-toxin; the negative phase being the period following an injection of tuberculin in which the patient's anti-toxin, having been used up by the toxin resulting from the injection, and not yet fully replaced by new anti-toxin, is less than it was at the time of the injection; and the positive phase being the period following the negative phase, in which the anti-toxin present exceeds what existed at the time of the inoculation, rising to a maximum and then gradually falling.

Now let us illustrate these phases by a curve with a downward bend followed by an upward one which reaches a maximum and then dies away as in the figure—



the horizontal dimension representing time, and the vertical dimension representing the quantity of anti-toxin present at the corresponding time.

Now let A and B be two points on the part of the curve representing the positive phase, equally distant from the base line, A being in the ascending part and B in the descending part. Then for the purpose of increasing tolerance of tuberculin in the shortest time, it would be better to give the next dose at A than at B ; but for procuring healing of the lesion it would be much better to give it at B. For it is during the positive phase that healing of the lesion may be expected to take place, and therefore, it is desirable, once the temperature has been controlled, to allow the patient a large amount of positive phase after each dose.

It is obviously undesirable to give a dose during the negative phase, as defined above, of the preceding dose : and there appears to be a general agreement among workers that one day intervals are too short, even with the smallest doses.

It is also clear that the negative and positive phases following an injection are of longer duration with large doses than with small ones. This is generally recognised by workers as a general principle : but, in my opinion, the extent to which this lengthening takes place is not sufficiently realized.

Thus, Camac Wilkinson says : "I rarely wait more than seven or eight days, except in the case of the larger doses (2 c.c., 3 c.c. or 4 c.c. of T.E.) ;" and "after a fortnight's interval it is not wise to increase the dose."

Riviere and Morland do not recommend extending the interval beyond a week until what they call "the maximum dose" has been reached. They recommend increasing it then, by degrees, to a month.

Bandelier and Roepke recommend that with doses of T. ·1 c.c. and more, the interval should be four to seven days. With a "maximal" dose of T. 1 c.c., however, they gradually increase the interval to a fortnight ; and with a "maximal" dose of T.R. 2 c.c. they increase it to six or eight weeks.

Bardswell does not appear to have used intervals longer than ten days, and seldom so long.

I find that I get good results by using the following :—

SCALE OF INTERVALS.

Dose.	Interval.
Not exceeding P.T.O. ·0001 c.c.	3 to 4 days : *i.e.*, injections are given twice a week.
P.T.O. ·0001 c.c. to ·01 c.c.	One Week.
P.T.O. ·01 c.c. or T. ·0001 c.c. to T. ·001 c.c.	Two Weeks.
T. ·001 c.c. to ·01 c.c.	Three Weeks.
T. ·01 c.c. to ·1 c.c.	Four Weeks.
Above T. ·1 c.c.	Six Weeks.

Of course, if any injection be followed by a rise of temperature above 99° F., the next dose is not given until at least one day has passed without the temperature so rising.

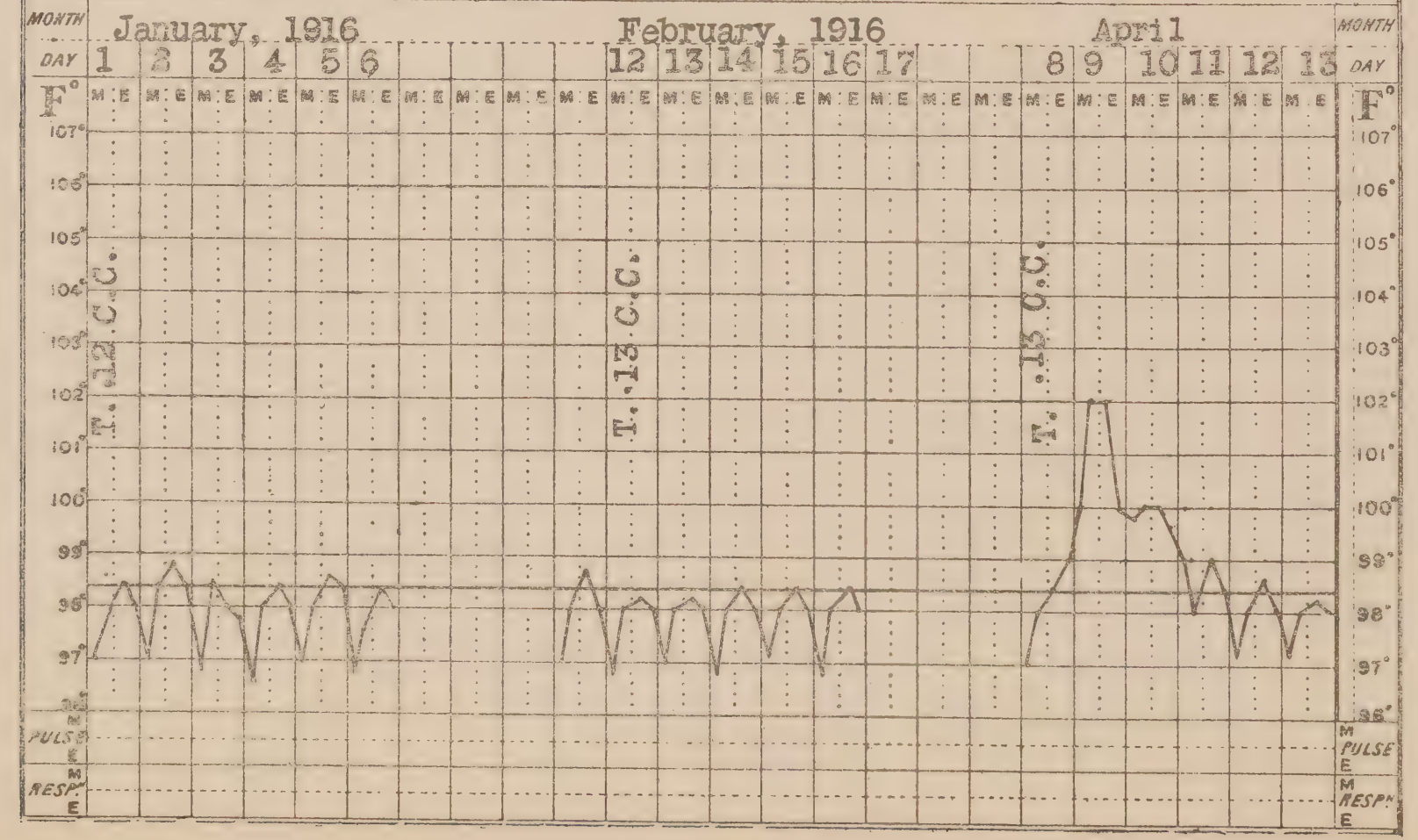
That the positive phase, as defined above, following doses from T. ·1 c.c. up has not concluded at the end of six weeks, is shewn by the fact that at the end of that time the dose can be increased without producing any febrile reaction, as I have repeatedly verified. This is well shewn by Chart No. II., uneventful portions of which have been omitted in order to bring the essential portions together. No injection was given between 1st January and 12th February, so that the interval was six weeks, and though the dose was increased no febrile reaction was produced.

The next interval was eight weeks, 12th February to 8th April, the patient having forgotten to come on the proper day. On this account the dose was not increased, but the repetition of the previous dose was followed by a sharp febrile reaction. Owing to this experience, I have not tried extending the interval between doses beyond six weeks. Fortunately the sharp febrile reaction experienced by the patient in this case did him no apparent harm, and he has since been discharged, after three years' treatment, free of all signs and symptoms of disease, though he had tubercle bacilli in his sputum throughout the first of the three years.

Temperature Chart, &c.

No. II

Name of Patient H.S.



The extension of the interval in some such manner as is recommended above has several advantages :—

1. In confirmation of the hope that by lengthening the proportion of time spent in positive phase, healing would be more likely to occur, I have found that in numerous cases improvement was much more noticeable after the interval had been increased to a fortnight than before, and then went steadily on. In some of these cases there was so little improvement in the early part of the course that there was some difficulty in persuading the patients to continue attendance.

2. It interferes so little with a patient's work to come once in four or six weeks for an injection, that those who have recovered so far as to return to work can be more easily persuaded to continue the treatment till the cure is complete, or indefinitely if complete cure is not to be looked for, than if they had to continue coming once a week.

3. One is enabled by this method to keep patients continuously under the beneficial effects of tuberculin treatment for long periods without reaching inconveniently large and expensive doses. I have never had to exceed T. ·2 c.c. even with patients whose treatment continued for over four years. When the interval is very long there may be more danger of the patient forgetting to come on the proper day, as in the case quoted above, but this can be obviated by indicating on his temperature card the day when he is to return.

Ratio of Increase of Doses.

Consideration of the anti-toxin curve given above will make it clear that the ratio of the amounts of an adjacent pair of optimum doses will depend on the interval of time between them.

If the time of an injection coincide with the time when the anti-toxin resulting from its predecessor is at its maximum, then a greater increase of dose can be borne, and is desirable, than if the interval between the doses were either greater or less.

When the anti-toxin is near its maximum, however, its amount changes very slowly. And when the dose is small, up to P.T.O. ·0001 c.c., this maximum probably occurs about the third or fourth day after the injection, which would explain how it is that the same ratio of increase can usually be employed after the three and four day intervals which recur in dispensaries that are open only twice a week.

But with any particular interval separating the injections, the ratio of increase of dose that best suits the case has to be found out in each case by experiment, and should be constantly under revision.

It has been shewn above, under the heading "Useful Doses," that at any time in a patient's history a beneficial dose must lie between narrow limits, and that the optimum dose is one that falls but little short of producing febrile reaction.

Fortunately there are definite indications which usually give warning to a careful worker when he is in danger of overstepping the mark and causing febrile reaction. These have been already referred to, but it is well to emphasize them at this point. They are

(*a*) Local Reaction.
(*b*) Elevation of Temperature to a point not exceeding 99° F.
(*c*) "Flattening of the temperature chart."

On the appearance of any of these indications the ratio of increase of doses which one has been using should be slightly diminished.

By observance of this rule one can almost entirely avoid the production of febrile reactions, at any rate of severe ones.

When a febrile reaction does occur I follow the usual practice of repeating the same dose till it can be borne without febrile reaction. After such an experience I increase the dose

by a slightly smaller ratio than that which led up to the reaction. Of course, if repetition of a dose which produced a reaction, produce a greater reaction, the dose is diminished in accordance with the rule given above under the heading "Hypersensitiveness."

On the other hand, when a few doses given at a certain rate of increase have produced no local reaction, and no appreciable effect on the temperature, the ratio of increase of doses should be gradually increased. By observance of this rule one avoids the danger of giving doses so small as to be of little or no benefit. It will thus be seen that no rule of thumb method of increasing doses, such as that laid down by Bandelier and Roepke, can be expected to give the best results. Bandelier and Roepke's ratios, which were used with slight modification by Bardswell, have the obvious defect that they vary, not because of anything in the patient's condition, but to suit the marks on the barrel of the syringe. The same objection applies to rules for increasing doses which are followed by many other workers.

But apart from this, my experience plainly indicates that :—

1. There is no fixed ratio of increase that will suit all cases.
2. The ratio of increase that is most suitable for a paient at one part of his course, is often not the most suitable at another part.
3. At any particular part of the course, the ratio that suits one patient best may not suit another patient at all.

In some cases I have found that during part of the course doses could only be increased with safety by the addition of 1/10th of the previous dose, or less : whereas in the same cases at another part of the course additions of 1/5th, 1/4th, or 1/3rd of the preceding dose were made with advantage.

Instances in which one-half of the preceding dose could be given with advantage have been comparatively rare in my

experience ; but in one case the fraction of the preceding dose that has been added each time has been gradually increased to two-thirds, and in another case three-fourths, with obvious advantage to the patients.

"Sensitiveness During Treatment" and "Limit of Tolerance."

That those workers who apply the same rule of increase to all cases manage sometimes to give a long series of doses without producing severe febrile reactions, is, in my opinion, evidence rather of the adaptability of the human body to circumstances, than of wisdom on the part of the operators.

When the rule of thumb breaks down when moderately high doses have been reached, Bardswell ascribes the difficulty to "Sensitiveness during Treatment," which, he says, can often be got over by careful management in the matter of repeating the doses, lengthening the intervals, or going back to a smaller dose. An additional expedient, viz., that of reducing the ratio of increase of dose, does not seem to have occurred to him. When the breakdown occurs when "the stronger doses" have been reached, i.e., "when the doses are being measured from the dilutions of 1 in 10, or even 1 in 100, Bardswell comes to the conclusion that the "Limit of Tolerance" has been reached.

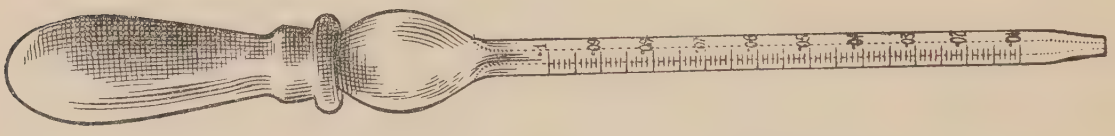
Lengthening the intervals according to the scale given above, and adjusting the ratio of increase of doses as occasion requires, I have never had any experience of this so-called "Limit of Tolerance," which does not differ in any essential way from "Sensitiveness during Treatment."

Method of Measuring Doses.

In order to be able to increase doses by small amounts with accuracy, and to vary the rate of increase by fine degrees, a more accurate instrument for measuring doses is required than that commonly in vogue, viz., the barrel of the syringe.

I have therefore had special pipettes for the purpose made to my order by Down Bros., London. These may be

briefly described as Wright's pipettes made of a special glass which can be heated in the flame of a spirit lamp without cracking. They are graduated on the stem as shown in the figure.



(Reduced).

The graduated portion holds 1-10th of a c.c., and is sub-divided, as shown in the figure into tenths and hundredths. The smallest divisions therefore hold a cubic millimetre.

The smallest divisions are not continued below the mark ·01 c.c. in order to diminish the liability to cracking; for though the glass is not supposed to crack in the flame of the spirit lamp, ultimately it does crack.

Technique.

The dilutions of tuberculin do not require special description, as they are made in the ordinary way, in descending powers of ten, with the diluting fluid, viz., a sterilised aqueous solution, containing ·8% of sodium chloride and ·5% of phenol. They are kept in glass-stoppered bottles.

The patient's temperature record since last visit, with his weight and pulse-rate, having been entered on the chart, the dose is decided on, and also entered on the chart.

A Record syringe having been already sterilised by boiling, the piston is inserted and pushed home; then the platinum needle is held in the flame of the spirit lamp till it is red-hot, when the piston is withdrawn. This ensures that the inside of the needle is dry, and that so the liquid put into the syringe from the pipette will not drip away through the needle before the piston is inserted.

The pipette is then taken from the sterilising tray and its stem moved about through the spirit lamp flame, the nipple being meanwhile compressed and relaxed alternately, till the

stem is seen to be dry both inside and out. By this means two ends are secured—(1) perfect sterilisation of the pipette, and (2) removal from the calibre of the tube of water which, filling an unknown fraction of it, would interfere with accurate measurement.

The dose is now taken from the appropriate bottle with the pipette and transferred to the syringe. The stem of the pipette is then filled with diluting fluid which is transferred to the syringe ; and this is repeated a second time. One thus ensures that the whole of the dose of tuberculin is washed down to the lower part of the barrel of the syringe, and that there is plain diluting fluid above to wash it all out when the piston is inserted. The back of the patient's arm having been prepared by rubbing it with methylated spirit on cotton wool, the skin is pinched up and the needle thrust into the subcutaneous tissue. The piston is then inserted into the barrel of the syringe. It compresses the air in the upper part of the barrel, and so drives the liquid below into the patient's arm without touching the liquid.

The needle is then withdrawn, and the puncture sealed with collodion.

By the above method one can be sure that the dose has been accurately measured, and that the whole of it has entered the patient's body.

That the precautions against sepsis are sufficient is shown by the fact that after many thousands of inoculations thus carried out, I have not known suppuration at the site of inoculation to occur once.

Duration of Treatment.

If possible the treatment should be continued till all signs of active tuberculosis, and all symptoms of the same, have disappeared, and at least three months longer. In the case of those patients whose "physical signs" do not disappear, but the temperature has been controlled, control of the temperature should be maintained by continuing the administration of tuberculin indefinitely.

With the scale of intervals given above this requires ultimately only one injection in six weeks, so the continuance of treatment is neither troublesome nor expensive.

With the long interval a very small ratio of increase of dose is required. It has been mentioned above that I have not hitherto had to give doses larger than T. ·2 c.c. . But if a case were to arise in which the principles above laid down led to a larger dose being required, a further lengthening of the interval to seven or eight or more weeks would be adopted.

Workers who do not lengthen the intervals as above, often go on increasing the dose till they reach 1 c.c. of whatever variety of tuberculin they happen to be using. This they call the "maximum" or "maximal" dose for some reason, apparently because that is as much as they can measure with their syringe at one operation. Bandelier and Roepke give the "maximal dose" of T. as 1 c.c., and of T.R. as 2 c.c. without stating any reasons.

When the "maximal dose" has been reached, some workers, as has already been mentioned, repeat this dose at gradually increasing intervals. This method has something to commend it; but, in my opinion, it is very much better to use long intervals long before such a dose is reached.

Other workers, having reached the "maximal dose" change the variety of tuberculin, and begin over again with small doses. From the principles laid down in this paper, it will be evident that this method has nothing to commend it. The early doses of the second series, being far below the equivalent of the anti-toxin produced in consequence of the first series, will, as explained under the heading "Too small Doses," have no useful effect, and may have a harmful one.

If the dose of tuberculin be in danger of becoming inconveniently large, and one decide to change to a stronger variety, the reduction in volume of dose should correspond as nearly as can be determined to the increase in strength of the new variety. Thus in changing from P.T.O. to T., I count that the latter is 100 times as strong as the former, and reduce the dose accordingly. In one case I reckoned it

as only 50 times as strong, with the result that a febrile reaction was produced.

Results.

It may be well to indicate in a general way the conditions under which the work, results of which are given below, has been carried on.

There are in County Down five Tuberculosis Dispensaries, under the care of the Tuberculosis Medical Officer and his Assistant, to which any person supposed to be suffering from tuberculosis may come for advice ; and, if circumstances be suitable, for treatment ; whether he or she be insured under the National Health Insurance Acts or not.

Roughly, it may be said that one-fourth of the population of the county live within convenient distance of a Tuberculosis Dispensary.

Nearly all the patients who come to these dispensaries are sent, in the first instance, by medical practitioners.

In all pulmonary cases treated at the dispensaries tuberculin has been administered on the lines laid down above.

Treatment at the dispensaries is the only form of treatment that the Tuberculosis Medical Officer has to offer to uninsured persons.

But for insured persons there are special arrangements. If they live within convenient distance of one of the dispensaries, and are afebrile, or can be made so by rest and graduated exercises, they are given their choice of dispensary or sanatorium treatment. Afebrile patients who do not live within convenient distance of a dispensary are given their choice of sanatorium or domiciliary treatment. Febrile patients who cannot be made afebrile, or until they become so, are given domiciliary treatment no matter what part of the county they live in. The sanatoria to which patients are sent are Forster Green Hospital, Belfast, and the Royal National Hospital for Consumption, Newcastle, Co. Wicklow. In the former, tuberculin has hardly been used in any of the cases which figure in the appended tables. In the latter, it has been administered according to a rule of thumb method,

doses being increased by the ratios represented by the figures 1, 2, 4, 6, 8, 10, repeated over and over again.

The figures for the two sanatoria have not been separated, as the numbers are so small that further subdivision would render percentages derived from them valueless.

No attempt was made to select more hopeful cases for the dispensaries than for the sanatoria, or *vice versa*. Those that were considered suitable for the one were considered suitable for the other, and the choice was left in each case to the patient.

Patients sent to sanatoria were kept there in every case as long as the Resident Medical Officer advised, if they were willing to stay. Some left contrary to advice, but similarly many of the patients who attended the dispensaries ceased attendance of their own accord instead of keeping on till they were discharged.

As a rule, patients who received sanatorium treatment were given domiciliary or dispensary treatment after their return.

In the appended tables the cases in which both sanatorium and dispensary treatment were received for at least three months each have been kept separate, and are not included with either the sanatorium or the dispensary cases proper. But the numbers in this little group are so small that the percentages derived from them have little value.

In March, 1917, I endeavoured to trace all patients diagnosed in 1913, 1914, and 1915 by myself or my assistants as suffering from pulmonary tuberculosis, and the results of this investigation are set forth in tables A, B and C respectively.

Eight cases diagnosed in 1912 have been included with the 1913 cases.

The attempt to trace these patients failed in only eight cases, *viz.*, six of the 1913 cases and one each of the 1914 and 1915 cases. These eight cases have not been included.

The Turban-Gerhardt system of classification of cases according to the extent and severity of "physical signs" having been adopted from the first, the stage under this

system was recorded on each patient's chart at the time of his first examination by one of the Tuberculosis Medical Officers as T.G. 1, 2 or 3. In the tables A, B and C, the cases in each group are divided up accordingly, as indicated by the column T.G. .

In a number of instances, particularly in the case of children, a diagnosis of pulmonary tuberculosis was made although no "physical signs" were observed. These were classified as T.G.0. They have not been included in the tables given below. It may be mentioned, however, that of these patients, none who were treated at the dispensaries had died, and all but one of them were at school or other work, in March, 1917 ; while of those not so treated 42·8% had died.

In the tables no case is included among the sanatorium or dispensary cases unless at least three months' continuous treatment was received there ; so that the class called "All others" contains many cases in which some sanatorium or dispensary treatment was given.

But a class containing cases that were past hope of recovery when first seen, and cases of "galloping consumption," would not make a useful basis of comparison for estimating the value of sanatorium and dispensary treatment. By excluding from the group "All others" all cases in which death occurred within six months from the time when the patients were first examined by the Tuberculosis Medical Officer or his Assistant, nearly all the cases that were hopeless from the first are eliminated, and the residue afford a very good basis of comparison. This is how group IV. in the tables has been arrived at.

For convenience, the time when a patient was first examined by the Tuberculosis Medical Officer or his Assistant, is called the time of "notification," this being the earliest date recorded in the ledger in connection with the patient's name. The word "notified" is used in a similar sense. The number and percentage of patients thus notified in each year, who died within six months of notification, was as follows :

Year.	Total Number of Cases.	Cases in which death occurred within six months.	
		No.	%
1913	161	38	23·6
1914	167	34	20·4
1915	154	48	31·2

The high proportion of deaths occurring within six months of notification in the 1915 cases as compared with the 1913, and especially the 1914 cases, suggests an explanation of a fact which appears puzzling when Tables B and C are compared, *viz.*, that in March, 1917, there were more of the 1914 patients at work than of the 1915 ones. The explanation would appear to be that the type of the disease as it attacked patients in 1915 was more severe than that of 1914. But this is by the way.

In the Tables then we have four groups, according to the treatment received, *viz* :—

1. Sanatorium, at least three months.
2. Dispensary, at least three months.
3. Sanatorium and Dispensary, at least three months each.
4. All others, excluding cases where death occurred within 6 months of notification.

In each of these groups is given the number of patients seen in each year who were in each of the three Turban-Gerhardt stages when first seen; and the number and percentage of these who were respectively at work, unfit to work, and dead, in March, 1917. The totals in each group are also given.

The portion of each table on the upper half of the page shews the numbers obtained by including cases in which tubercle bacilli were not found in the sputum, as well as those in which they were found. The lower portion shews the smaller figures obtained by including only those cases in which tubercle bacilli were found in the sputum. Whether we consider the

percentage of patients at work, or the percentage dead, the sanatorium figures are better than those of group IV. in almost every instance; exceptions occurring only in places where the numbers are so small that the percentages are of little value.

But the superiority of the dispensary figures is much greater. If we count only the percentage at work and the percentage dead (neglecting the percentage unfit for work), there are forty-eight percentages given in Tables A, B and C in connection with each of the groups I., II., III., and IV. If we arrange groups I., II., and IV. in order of merit in respect to each of these percentages, group II. (dispensary) takes first place forty-six times, and second place in the other two.

The two instances in which group II. does not take first place are in Table B, one in the upper, and one in the lower half. In both instances the actual figures are small, so that the percentages are of small value.

This almost invariable superiority of the dispensary percentages appears to justify the conclusion that tuberculin, when administered on the lines laid down in this paper, is of distinct service in the treatment of pulmonary tuberculosis.

TABLE A.

CASES OF PULMONARY TUBERCULOSIS NOTIFIED IN 1913.

T.B.	Mode of Treatment	T.G.	No. of Cases	Condition in March, 1917. At Work No.	At Work %	Unfit for Work No.	Unfit for Work %	Dead No.	Dead %
	I. Sanatorium, at least 3 months	1	5	3	60	–	0	2	40
		2	–	–	–	–	–	–	–
		3	9	2	22·2	–	0	7	77·8
		Total	14	5	35·7	–	0	9	84·3
+	II. Dispensary, at least 3 months	1	21	17	81	1	4·8	3	14·2
		2	4	1	25	1	25	2	50
		3	23	6	26·1	–	0	17	73·9
		Total	48	24	50	2	4·2	22	45·8
&	III. Sanatorium and Dispensary, at least 3 months each	1	4	2	50	–	0	2	50
		2	1	–	0	–	0	1	100
–		3	5	2	40	2	40	1	20
		Total	10	4	40	2	20	4	40
	IV. All others, excluding cases where death occurred within six months of notification	1	11	5	45·5	1	9·1	5	45·4
		2	4	–	0	–	0	4	100
		3	36	5	13·9	–	0	31	86·1
		Total	51	10	19·6	1	2	40	78·4
	I. Sanatorium, at least 3 months	1	4	2	50	–	0	2	50
		2	–	–	–	–	–	–	–
		3	6	–	0	–	0	6	100
		Total	10	2	20	–	0	8	80
+	II. Dispensary, at least 3 months	1	7	4	57·1	–	0	3	42·9
		2	3	1	33·3	–	0	2	66·7
		3	16	2	12·5	–	0	14	87·5
		Total	26	7	26·9	–	0	19	73·1
	III. Sanatorium and Dispensary, at least 3 months each	1	3	1	33·3	–	0	2	66·7
		2	1	–	0	–	0	1	100
		3	2	1	50	–	0	1	50
		Total	6	2	33·3	–	0	4	66·7
	IV. All others, excluding cases where death occurred within six months of notification	1	3	1	33·3	–	0	2	66·7
		2	3	–	0	–	0	3	100
		3	18	–	0	–	0	18	100
		Total	24	1	4·2	–	0	23	95·8

TABLE B.

CASES OF PULMONARY TUBERCULOSIS NOTIFIED IN 1914.

T.B.	Mode of Treatment	T.G.	No. of Cases	Condition in March, 1917. At Work No.	At Work °/₀	Unfit for Work No.	Unfit for Work °/₀	Dead No	Dead °/₀
—	I. Sanatorium, at least 3 months	1	2	1	50	1	50	–	0
		2	–	–	–	–	–	–	–
		3	11	3	27·3	2	18·2	6	54·5
		Total	13	4	30·8	3	23·1	6	46·1
+	II. Dispensary, at least 3 months	1	9	6	66·7	2	22·2	1	11·1
		2	6	4	66·7	1	16·7	1	16·6
		3	16	11	68·75	2	12·5	3	18·75
		Total	31	21	67·8	5	16·1	5	16·1
&	III. Sanatorium and Dispensary, at least 3 months each	1	–	–	–	–	–	–	–
		2	1	–	0	1	100	–	0
		3	5	3	60	1	20	–	20
		Total	6	3	50	2	33·3	1	16·7
–	IV. All others, excluding cases where death occurred within six months of notification	1	13	8	61·5	–	0	5	38·5
		2	10	3	30	–	0	7	70
		3	60	22	36·7	2	3·3	36	60
		Total	83	33	39·8	2	2·4	48	57·8
—	I. Sanatorium, at least 3 months	1	–	–	–	–	–	–	–
		2	–	–	–	–	–	–	–
		3	8	1	12·5	2	25	5	62·5
		Total	8	1	12·5	2	25	5	62·5
	II. Dispensary, at least 3 months	1	4	2	50	1	25	1	25
		2	2	1	50	–	0	1	50
		3	7	4	57·1	2	28·6	1	14·3
		Total	13	7	53·8	3	23·1	3	23·1
+	III. Sanatorium and Dispensary, at least 3 months each	1	–	–	–	–	–	–	–
		2	1	–	0	1	100	–	0
		3	3	1	33·3	1	33·3	1	33·3
		Total	4	1	25	2	50	1	25
	IV. All others, excluding cases where death occurred within six months of notification	1	3	2	66·7	–	0	1	33·3
		2	4	–	0	–	0	4	100
		3	28	2	7·1	1	3·6	25	89·3
		Total	35	4	11·4	1	2·9	30	85·7

TABLE C.

CASES OF PULMONARY TUBERCULOSIS NOTIFIED IN 1915.

T.B.	Mode of Treatment	T.G.	No. of Cases	Condition in March, 1917					
				At Work		Unfit for Work		Dead	
				No.	%	No.	%	No.	%
	I. Sanatorium, at least 3 months	1	3	1	33·3	1	33·3	1	33·3
		2	4	2	50	1	25	1	25
		3	10	4	40	2	20	4	40
		Total	17	7	41·2	4	23·5	6	35·3
+	II. Dispensary, at least 3 months	1	12	11	91·7	–	0	1	8·3
		2	6	4	66·7	1	16·7	1	16·7
		3	13	7	53·8	3	23·1	3	23·1
		Total	31	22	71	4	12·9	5	16·1
&	III. Sanatorium and Dispensary, at least 3 months each	1	–	–	–	–	–	–	–
		2	1	1	100	–	0	–	0
		3	4	2	50	2	50	–	0
		Total	5	3	60	2	40	–	0
–.	IV. All others, excluding cases where death occurred within six weeks of notification	1	12	7	58·3	2	16·7	3	25
		2	7	1	14·3	2	28·6	4	57·1
		3	34	6	17·6	7	20·6	21	61·8
		Total	53	14	26·4	11	20·8	28	52·8
	I. Sanatorium, at least 3 months	1	2	–	0	1	50	1	50
		2	2	–	0	1	50	1	50
		3	7	1	14·3	2	28·6	4	57·1
		Total	11	1	9·1	4	36·3	6	54·6
	II. Dispensary, at least 3 months	1	3	2	66·7	–	0	1	33·3
		2	2	1	50	1	50	–	0
		3	4	1	25	1	25	2	50
		Total	9	4	44·4	2	22·2	3	33·3
+	III. Sanatorium and Dispensary, at least 3 months each	1	–	–	–	–	–	–	–
		2	1	1	100	–	0	–	0
		3	2	1	50	1	50	–	0
		Total	3	2	66·7	1	33·3	–	0
	IV. All others, excluding cases where death occurred within six months of notification	1	2	–	0	–	0	2	100
		2	5	–	0	1	20	4	80
		3	16	–	0	5	31·25	11	68·75
		Total	23	–	0	6	26·1	17	73·9

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